Angiogenesis

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Angiogenesis is the physiological process involving the formation of new blood vessels from pre-existing vessels. It is of clinical relevance, being a fundamental step in the transition of tumors from a dormant state to a malignant state.

Cancer cells are cells that have lost control of their ability to divide in a controlled fashion. A tumor consists of a population of rapidly dividing and growing cancer cells. Mutations rapidly accrue within the population. These mutations (variation) allow the cancer cells (or sub-populations of cancer cells within a tumor) to develop drug resistance and escape therapy. Tumors cannot grow beyond a certain size, generally 1-2 mm^3, due to a lack of oxygen and other essential nutrients.

Tumors induce blood vessel growth (angiogenesis) by secreting various growth factors (e.g. Vascular Endothelial Growth Factor or VEGF). Growth factors, such as bFGF and VEGF can induce capillary growth into the tumor, supplying required nutrients and allowing for tumor expansion. Thus angiogenesis is a necessary and required step for transition from a small harmless cluster of cells, to a large tumor. Angiogenesis is also required for the spread of a tumor, or metastasis. Single cancer cells can break away from an established solid tumor, enter the blood vessel, and be carried to a distant site, where they can implant and begin the growth of a secondary tumor. Evidence now suggests that the blood vessel in a given solid tumor may be in fact be mosaic vessels, comprised of endothelial cells and tumor cells. This mosaicity allows for substantial shedding of tumor cells into the vasculature. The subsequent growth of such metastases will also require a supply of nutrients and oxygen.

Endothelial cells are much more genomically stable than cancer cells, and have a doubling time of approx 120 days. The genomic stability allied to their longevity (compared to the tumor cell), makes then an ideal target for therapies directed against them. They will not 'escape' therapy, as they will not undergo mitosis at such a rapid rate and carry any drug resistance variation through to the next generation within the lifespan of the therapy.

Angiogenesis research is a cutting edge field in cancer research, and recent evidence also suggests that traditional therapies, such as radiation therapy, may actually work in part by targetting the genomically stable endothelial cell compartment, rather than the genomicaly unstable tumor cell compartment. In short, the therapy is the selection agent which is being used to kill a cell compartment. Tumor cells evolve resistance rapidly due to rapid generation time (days) and genomic instability (variation), whereas endothelial cells are a good target because of a long generation time (months) and genomic stability (low variation).

This is a prime example of evolution in action at the cellular level, using a selection pressure to target and differentiate between varying populations of cells. The end result is the extinction of one species or population of cells (endothelial cells), followed by the collapse of the ecosystem (the tumor).

Angiogenesis-based tumour therapy relies on the existence of natural angiogenesis inhibitors like angiostatin , endostatin and tumstatin. These are proteins that mainly originate as specific fragments pre-existing structural proteins like collagen or plasminogen.